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Hypocalcemia in trauma patients: A systematic review

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BACKGROUND: During hemorrhagic shock and subsequent resuscitation, pathways reliant upon calcium such as platelet function, intrinsic and extrinsic hemostasis, and cardiac contractility are disrupted. The objective of this systematic review was to examine current literature for associations between pretransfusion, admission ionized hypocalcemia, and composite outcomes including mortality, blood transfusion requirements, and coagulopathy in adult trauma patients.

METHODS: This review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. We searched Ovid MEDLINE and grey literature from database inception till May 3, 2020. Case series and reports were excluded. Reference lists of appraised studies were also screened for articles that the aforementioned databases might not have captured. The Newcastle-Ottawa Scale was used to assess study quality.

RESULTS: A total of 585 abstracts were screened through database searching and alternative sources. Six unique full-text studies were reviewed, of which three were excluded. Admission ionized hypocalcemia was present in up to 56.2% of the population in studies included in this review. Admission ionized hypocalcemia was also associated with increased mortality in all three studies, with increased blood transfusion requirements in two studies, and with coagulopathy in one study.

CONCLUSION: Hypocalcemia is a common finding in shocked trauma patients. While an association between admission ionized hypocalcemia and mortality, blood transfusion requirements, and coagulopathy has been identified, further prospective trials are essential to corroborating this association. (*J Trauma Acute Care Surg.* 2021;90: 396–402. Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.)

LEVEL OF EVIDENCE: Systematic review, level III.

KEY WORDS: Hypocalcemia; hemorrhagic shock; mortality; coagulopathy; transfusion.

Uncontrolled exsanguinating hemorrhage after traumatic injury remains the most common cause of potentially preventable death,[1] with 11% of all mortality and 13% of disability-adjusted life years globally attributed to injury.[2] Death from hemorrhagic shock occurs rapidly within 2 to 6 hours postinjury,[3–5] necessitating expeditious resuscitative strategies through a combination of hemostatic interventions and timely blood product administration.[6]

During hemorrhagic shock and subsequent resuscitation, pathways reliant upon calcium such as platelet function, intrinsic and extrinsic hemostasis, and cardiac contractility are disrupted.[7,8] It has been suggested that, in hemorrhagic shock, hypocalcemia may result from intracellular flux secondary to ischemia and reperfusion.[9,10] While blood components including ions such as calcium are lost in hemorrhagic shock,[11] impaired calcium homeostasis and increased sympathetic activity also contribute to hypocalcemia in critically ill patients.[12] Citrate containing products such as packed red blood cell and fresh frozen plasma are also known to perpetuate hypocalcemia during resuscitation,[13] especially in shocked patients unable to metabolize citrate adequately because of reduced hepatic function secondary to hypoperfusion and hypothermia.[14,15] Current literature has highlighted the pervasiveness of hypocalcemia as a metabolic derangement in critically ill patients, with incidence as high as 97.3%.[16] It is therefore hypothesized that timely recognition and correction of hypocalcemia in the hemorrhaging major trauma patient may ameliorate such disruptions while also augmenting hemostatic, ionotropic, and chronotropic mechanisms.[17]

Current literature has focused on the effects of transfusion-induced hypocalcemia on hemorrhagic shock, while evidence on pretransfusion, hemorrhage-induced hypocalcemia, and impairments in calcium homeostasis are scant. The objective of this systematic review was to examine current literature for associations between pretransfusion, admission ionized hypocalcemia, and composite outcomes including mortality, blood transfusion requirements, and coagulopathy in adult trauma patients.

PATIENTS AND METHODS

This study was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Fig. 1) (http://links.lww.com/TA/B849),[18] which has been included in Appendix (PROSPERO Review Protocol and Registration, CRD42020105135).

Search Strategy

This systematic review searched English and non-English literature. Subject headings (/) were used in the following way: (Calcium/bl, df [Blood, Deficiency] or Hypocalcemia/bl, co, mo [Blood, Complications, Mortality]) *and* (shock/or shock, hemorrhagic/or shock, traumatic/or Critical Illness/or "wounds and injuries"/or abdominal injuries/or amputation, traumatic/or back injuries/or contrecoup injury/or crush injuries/or foreign bodies/or fractures, bone/or multiple trauma/or neck injuries/or shock, traumatic/or spinal cord injuries/or thoracic injuries/or war-related injuries/or wounds, nonpenetrating/or wounds, penetrating/). Key words ("") were used in conjunction with the "adjacent to one another within 5 words" function in the following way: ((hypocalc?emi* or ioni?ed calcium or ioni?edhypocalc?emia) adj5 (traum* or shock* or critical* ill*)).mp. Because of the paucity of current literature on the topic, we chose not to apply further limits to our studies, instead manually excluding studies as described hereinafter.

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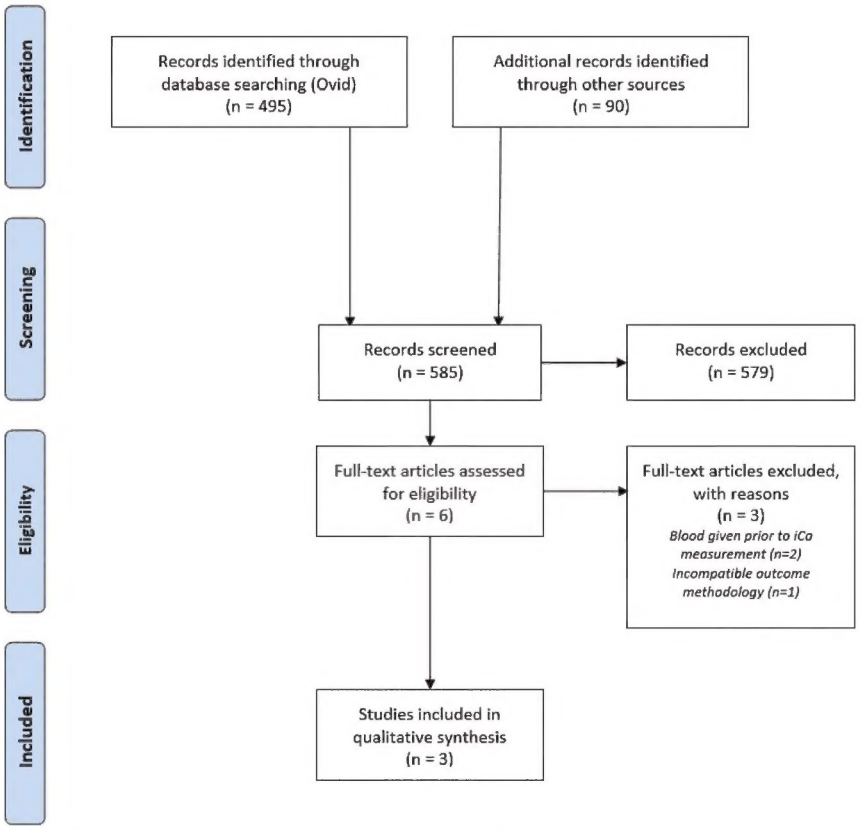
Identification
Screening
Eligibility
Included
Records identified through database searching (Ovid) (n = 495)
Additional records identified through other sources (n = 90)
Records screened (n = 585)
Records excluded (n = 579)
Full-text articles assessed for eligibility (n = 6)
Full-text articles excluded, with reasons (n = 3)
Blood given prior to iCa measurement (n=2)
Incompatible outcome methodology (n=1)
Studies included in qualitative synthesis (n = 3)

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Eligibility Criteria

We included all trauma patients 18 years or older with an admission ionized calcium measurement before blood transfusion and all study types except case reports and series and studies on animals.

Exclusion Criteria

We excluded studies where patients had received blood products before the initial ionized calcium measurement, because of the well-known phenomenon of transfusion-induced hypocalcemia.[19] Studies where ionized calcium concentrations were not obtained on arrival before blood transfusion were also excluded to maintain methodological consistency.

Information Sources

We searched for articles from Ovid MEDLINE extending from its commencement to May 3, 2020. We also screened reference lists of numerous studies for relevant articles that might not otherwise have been captured.

Study Selection

Following the search, duplicates were removed, and titles were subsequently appraised for eligibility independently by two authors (M.V. and J.K.M.). The abstracts of the selected titles were read, and full texts were sought for articles meeting the inclusion criteria. Reference lists of relevant articles were checked for additional studies.

Data Extraction

We extracted data including hospital setting, study type, country of treatment, cohort size, incidence of admission ionized hypocalcemia, ionized hypocalcemia definitions, and the following outcomes: mortality, blood transfusion requirements, and coagulopathy.

Assessment of Quality

We used the Newcastle-Ottawa Scale[20] to assess the quality of selected studies.

RESULTS

A total of 585 abstracts were screened through database searching and alternative sources. Six unique full-text studies were reviewed, of which three were excluded. Study characteristics are

TABLE 1. Summary of Studies

Study Author	Country	Patient Cohort	Study Design
Cherry et al.[21]	United States	N = 396 Trauma center *LoCa ≤1.0 mmol/L	Retrospective cohort
Magnotti et al.[22]	United States	N = 591 Trauma center LoCa <1.0 mmol/L	Prospective cohort
Vasudeva et al.[23]	Australia	N = 226 Trauma center LoCa <1.11 mmol/L	Retrospective cohort

*LoCa — ionized hypocalcemia.

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TABLE 2. Results of Studies

Study Author	Outcomes of Interest
Cherry et al.[21]	Mortality: 26.4%* vs. 16.7%**; $p < 0.05$; OR, 1.92
Magnotti et al.[22]	Mortality: 15.5%* vs. 8.7%**; $p = 0.036$ Transfusion (≥5 U): 17.1%* vs. 7.1%**; $p = 0.005$ Transfusion (≥10 U): 8.2%* vs. 2.2%**; $p = 0.017$
Vasudeva et al.[23]	Mortality: 25.6%* vs. 15.0%**; $p = 0.047$ Transfusion: 62.5%* vs. 37.5%**; $p < 0.001$ Coagulopathy*: aOR, 2.9; 95% CI, 1.01–8.3; $p = 0.048$

*Hypocalcemic cohort.
**Normocalcemic cohort.
OR, odds ratio.

listed in Table 1, while a summary of the results has been tabulated in Table 2.

Admission ionized hypocalcemia (defined as ≤1.0 mmol/L) was associated with increased mortality and decreased time to death[21] in 396 American trauma patients by Cherry et al.[21] Twenty-three percent of the study population was hypocalcemic on admission. Mortality rates were 26.4% and 16.7% ($p < 0.05$; odds ratio, 1.92) in the hypocalcemic and normocalcemic groups, respectively.

Similarly, hypocalcemic trauma patients were found to experience a higher mortality rate (15.5% vs. 8.7%, $p = 0.036$) in a prospective study by Magnotti et al.[22] Hypocalcemia was also associated with a need for both multiple (17.7% vs. 7.1%, $p = 0.005$) and massive transfusions (8.2% vs. 2.2%, $p = 0.017$). Hypocalcemia was defined as <1.0 mmol/L, with 56.2% of the study population displaying this aberrancy on admission. Multiple transfusions meant being administered ≥5 U of packed red cells in 24 hours, while massive transfusions meant being administered ≥10 U in 24 hours. Hypocalcemia was identified as an independent predictor of the need for multiple transfusions after accounting for age and injury severity (adjusted odds ratio [aOR], 2.294; 95% confidence interval [CI], 1.053–4.996).

A retrospective study of 226 level 1 trauma patients in Australia by Vasudeva et al.[23] identified a higher mortality rate in the hypocalcemic cohort on hospital discharge (25.6% vs. 15.0%, $p = 0.047$). Requirement for blood transfusion was also associated with hypocalcemia (62.5% vs. 37.5%, $p < 0.001$). They also found hypocalcemia to be independently associated with coagulopathy (aOR, 2.9; 95% CI, 1.01–8.3; $p = 0.048$). In this study population, 50% of the study population was hypocalcemic, defined as <1.11 mmol/L.

Study Quality

Study selection, comparability of groups, and outcome ascertainment were assessed (S/C/O) with a total of eight items and a maximum score of 9 (S4/C2/O3).[20] We also assessed quality based on study design, blinding, and number of reviewers. The overall quality of the studies was moderate. Magnotti et al.[22] scored 7 over 9, Cherry et al.[21] scored 6/9, and Vasudeva et al.[23] scored 7/9. None of the studies were blinded nor explicitly stated the utilization of different reviewers for data collection and cross checking (Table 3).

DISCUSSION

This review identified three studies in Australia and United States with a total of 1,213 trauma patients. The studies identified an association between hypocalcemia and mortality, blood transfusion requirements, and coagulopathy. While Cherry et al.[21] noted an incidence of 23.0% hypocalcemia on admission, Magnotti et al.[22] and Vasudeva et al.'s[23] studies saw higher incidences at 56.2% and 50%, respectively. This is in keeping with other studies that have reflected admission hypocalcemia in up to 74% of the study population.[11]

Mortality

Higher mortality rates were observed in hypocalcemic patients in all three studies.[21–23] Not surprisingly, numerous other studies have identified such an association in similar patient populations.[24] For example, Ho and Leonard[25] identified a correlation between hypocalcemia and mortality in trauma patients requiring blood transfusions, while Vinas-Rios et al.[26] and Manuel et al.[27] identified hypocalcemia as a prognostic factor for early mortality in traumatic brain injury. While Ho and Leonard's[25] study was confounded by the prior use of blood products in resuscitation, their analysis did attempt to adjust for the use of packed red cells. Similarly, Choi and Hwang[16] identified hypocalcemia in adult trauma patients as a significant risk factor for mortality, albeit without excluding patients who had received blood products prior to ionized calcium measurement.

Vivien et al.,[11] in a separate prospective study of 212 severe patients of whom 64% were hypocalcemic, identified hypocalcemia as a prognostic factor for mortality with an inversely proportionate relationship between mortality and ionized calcium levels. In hypocalcemic trauma intensive care unit (ICU) patients, hypocalcemia tends not to normalize,[28] lending further credence to its prognostic value. A review of hemostasis in trauma by Lier et al.[29] found that ionized hypocalcemia of <1.0 mmol/L significantly increases patient mortality regardless of injury severity, with a threefold increase in mortality noted when ionized calcium concentrations trend below 0.88 mmol/L.

Transfusion Requirements

While Magnotti et al.[22] and Vasudeva et al.[23] were able to identify an association between hypocalcemia and blood transfusion requirements, the severity of hypocalcemia in critically

TABLE 3. Study Quality

Author	NOS Rating (S/C/O)	Study Design	Blinding	Number of Reviewers
Cherry et al.[21]	3/1/2	Retrospective cohort	No	Not explicitly stated
Magnotti et al.[22]	3/2/2	Prospective cohort	No	Not explicitly stated
Vasudeva et al.[23]	3/1/3	Retrospective cohort	No	Not explicitly stated

NOS, Newcastle-Ottawa Scale.

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ill trauma patients has previously been shown to parallel transfusion requirements.[24,30] Increased transfusion needs are also known to be an independent predictor of increased mortality[31,32] in trauma patients. This makes ionized calcium a useful adjunct to other biochemical markers such as base excess and lactate in the early phase of resuscitation and prognostication of trauma patients.[22]

Coagulopathy

Hypocalcemia was significantly associated with coagulopathy on arrival to the emergency department (odds ratio, 5.5; 95% CI, 2.8–10.8; $p < 0.001$) in Vasudeva et al.'s[23] study. A multivariate analysis including known associated clinical variables including Injury Severity Score, Glasgow Coma Scale, bicarbonate, and lactate identified an independent association between hypocalcemia and coagulopathy (aOR, 2.9; CI, 1.01–8.29). This is the only known study to have identified such an association in shocked trauma patients, lending credence to the previously proposed hypothesis associating hypocalcemia and poor clot strength[25] in critically ill patients. This is especially so for ionized calcium concentration levels of <1.0 mmol/L, with one study suggesting a cutoff of 0.9 mmol/L for hypocalcemia to influence coagulopathy.[33] The importance of this association is highlighted by studies that have identified coagulopathy in severely injured trauma patients before any blood product administration, which increases the risk of rapid exsanguination and death from hemorrhagic shock.[34,35] Nonetheless, consensus data on what constitutes a clinically symptomatic cutoff for ionized hypocalcemia are scant, with the European guidelines suggesting replenishment of calcium when ionized calcium levels fall below 0.9 mmol/L, albeit in the context of transfusion.[36] Furthermore, viscoelastic measurements may not directly highlight the negative impact of hypocalcemia on coagulation because of preanalysis blood sample recalcification, which makes ascertainment of a causative relationship challenging with standard viscoelastic testing.

Other Outcomes

No studies have examined the association between hypocalcemia and sudden cardiac arrest in critically ill trauma patients. However, ionized hypocalcemia on admission has been described in patients suffering from cardiac arrest by in a prospective series by Gando et al.[37] Hypocalcemia has also precipitated cardiac arrhythmias and frank cardiac failure in massive transfusion patients.[38,39] Vasopressor requirements can also be as high as 41% of hypocalcemic medical ICU patients as opposed to 14% in their normocalcemic counterparts.[40] Cherry et al.[21] were also able to appreciate the independent association between pre-hospital hypotension and hypocalcemia.

A 2020 review of two randomized controlled trials focusing on treatment of traumatic hemorrhagic shock with plasma identified a high risk of hypocalcemia in the plasma treatment arm, which was in turn associated with reduced survival and predictive of massive transfusion.[41] These findings are particularly important in the context of the increasing ubiquity of plasma-based resuscitation in high-risk trauma patients, further highlighting the dangers of hypocalcemia in the periresuscitative period.

The cyclical and self-perpetuating relationship between blood loss, hypocalcemia, and abnormal coagulation unsurprisingly leads to significant mortality with a shorter median time to death in hypocalcemic patients.[21] Because fluid resuscitation measures lead to hemodilution and exacerbate hypocalcemia, timely correction of hypocalcemia might arrest this vicious cycle and ameliorate mortality[24,42] related to exsanguination and end-organ damage in the critically ill trauma patient population. Nonetheless, it remains to be seen if this will impact length of hospital stay, as Cherry et al.[21] found no difference between hypocalcemic and normocalcemic bleeding trauma patients. However, in severe hypocalcemia, ICU length of stay is increased.[43]

Therapy

Replacement of blood loss is a cornerstone of management in trauma patients.[23] The European guideline on management of major bleeding and coagulopathy following trauma[36] recommends ionized calcium levels be monitored and maintained within the normal range during massive transfusion with appropriate administration of calcium chloride to correct hypocalcemia. The prevalence of hypocalcemia in up to 97% of trauma patients within 24 hours of massive transfusions[17] further highlights the importance of treating this aberrancy to ameliorate outcomes such as mortality, blood transfusion requirements, and coagulopathy.

While none of the studies included in this review studied the potential therapeutic benefit of timely correction of hypocalcemia in trauma patients, there is some evidence to suggest benefit in correction of hypocalcemia. In a retrospective review of 297 military combat trauma patients who received an average of 4 U of blood products before hospital admission, hypocalcemia was present in 28.3% of the cohort treated with 10 mL 10% intravenous calcium chloride, while hypocalcemia was evident in 70.0% of the nontreatment group.[42] In shocked patients requiring colloids, calcium-containing haemaccel infusions have been reliably found to increase ionized calcium concentrations.[44]

Although in the context of transfusion, Giancarelli et al.[17] identified a threshold of 0.9 mmol/L to commence calcium therapy in the form of 2 g of calcium chloride for every 2 to 4 U of blood products transfused given that even 1 U of blood can cause hypocalcemia in trauma patients.[42] Dickerson et al.[45] suggested a short-term infusion of 4 g of intravenous calcium gluconate for the treatment of moderate to severe hypocalcemia in critically ill, adult multiple injury patients. Correction of hypocalcemia in certain subsets of this patient population yields an improvement in left ventricular function and mean arterial pressure.[46,47]

Limitations

Hypocalcemia has only been sparsely studied in the context of trauma patients and even less so in patients whose calcium levels have not been confounded by prior blood transfusions. We therefore had to exclude several studies,[16,25] which examined the association between hypocalcemia and the composite outcomes discussed in this review. Our review is also subject to publication bias[48] because studies that did not identify an association between hypocalcemia and any of the aforementioned outcomes in critically ill trauma patients might simply not have been published.

In considering Magnotti et. al's[22] results, only 10% of the study population required massive transfusions. This reduces the predictive power of hypocalcemia and the need for massive transfusions in the critically ill trauma patient. Vasudeva et al.'s[23]

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study population was relatively small, with only 64 patients displaying coagulopathy. All three studies also failed to account for mechanistic variables such as coagulation factor levels and fibrinolysis, which could potentially confound the association between hypocalcemia and associated outcomes. These studies are observational and therefore only hypothesis generating, although providing ample clinical indication for protocolized calcium replacement in shocked patients through a randomized controlled trial.

It is also worth considering that a small subset of the critically ill trauma patient population might in fact suffer the often initially asymptomatic adverse effects of hypercalcemia including seizures and respiratory arrest,[49,50] although this has only been noted in patients who have been immobilized for several weeks and not lost significant quantities of blood. In such a patient population, prehospital correction of presumed hypocalcemia may be superfluous or potentially even dangerous. In traumatic brain injury patient populations, ionized hypocalcemia has also displayed a protective function through mitigation of intracellular calcium-induced apoptosis through reduced lipase activation and reduced inhibition of mitochondrial enzymatic processes.[26]

CONCLUSIONS

In conclusion, hypocalcemia is a common finding in shocked trauma patients, in whom death can occur rapidly. Review of current published literature indicates a focus on transfusion related hypocalcemia or its association with mortality without accounting for prior blood product administration. This systematic review has identified moderate quality evidence on the association between transfusion-independent hypocalcemia and mortality, blood transfusion needs, and coagulopathy. However, further prospective trials are needed to corroborate this relationship and identify possible therapeutic measures that might mitigate the aforementioned outcomes.

AUTHORSHIP

M.V., J.K.M., and M.C.F. conceived the study methodology and design. M.V. conducted the literature search with study selection performed with J.K.M. M.V. and J.K.M. analyzed the data and drafted the article. All authors contributed substantially to revision of the article. M.V. takes responsibility for the article.

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DISCLOSURE

The authors declare no conflicts of interest.

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